# STUDY PROTOCOL

## PROTOCOL TITLE:
Phacoemulsification versus phacoemulsification with micro-bypass stent implantation in primary angle closure and primary angle closure glaucoma: Randomized double-masked clinical trial

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# STUDY PROTOCOL

## 1. BACKGROUND AND RATIONALE

Glaucoma is a leading cause of irreversible blindness. The disease is characterized by elevated intraocular pressure (IOP), cupping of the optic disc, or a diminished visual field. Large prospective studies have shown that the risk for glaucomatous progression is significantly reduced when IOP is lowered and that each 1mmHg reduction in IOP is associated with an approximate 10% decrease in the risk for progression

It is firmly entrenched in the traditional treatment paradigm to start with pharmacotherapy. However, pharmacotherapy is not benign and has been well documented to have a number of significant challenges. Once medications have failed, the conventional next step is to perform a trabeculectomy operation which is a intraocular penetrating operation.

The iStent is a FDA and HSA approved micro-bypass stent device that is implanted with an ab interno approach (inserted from inside the eye rather than from outside the eye) that bypasses the trabecular meshwork (filtration membrane of the aqueous fluid exit pathway) and reroutes aqueous from the anterior chamber directly into canal of Schlemm and out of the eye without disrupting the conjunctival and scleral eye surface.

It works well in open angle glaucoma, where the drainage angle is open and has been shown to reduce the eye pressure and number of medications required at 2 years post operation. This device has not been used in angle closure glaucoma because of the lack of space when the drainage angle is narrow. However, if this device is combined with lens extraction or cataract surgery, then the drainage angle is widened and the device can be safely implanted.

Cataract surgery or phacoemulsification lens extraction is known to reduce the eye pressure in certain cases, but not all cases. It is more effective in IOP lowering in angle closure cases. It is not standard care to perform phacoemulsification lens extraction in angle closure glaucoma. The standard of care is usually a combined operation of phacoemulsification with trabeculectomy or trabeculectomy alone. Trabeculectomy, however, has a significant complication rate that includes infection, bleeding, bleb failure, bleb infections, hypotony and suprachoroidal haemorrhages.

The purpose of this study was to compare the IOP-lowering efficacy and safety of phacoemulsification alone and phacoemulsification and micro-bypass stent implantation in eyes with primary angle closure and primary angle closure glaucoma.

### 1.1. General Introduction

The iStent is a FDA and HSA approved micro-bypass stent device that lowers the IOP. It needs to be combined with phacoemulsification lens extraction in angle closure glaucoma in order to create enough space for the iStent to be safely inserted. Both phacoemulsification and phacoemulsification with iStent are likely to reduce the IOP, but we hypothesis that the combined group will perform better, leading to better IOP control using less medications at 1 year.

## 1.2. Rationale and justification for the Study

The iStent has never been studied in primary angle closure or primary angle closure glaucoma. In Singapore or Chinese populations, primary angle closure and primary angle closure glaucoma is much more common than in the African and Caucasian populations. All iStent studies have been in patients with open angles, which is more common in the West. We have therefore selected this population for our study, which is more relevant in the Singapore context.

It is becoming more popular to remove the lens with phacoemulsification in angle closure glaucoma as a form of treatment to reduce IOP. It works by increasing the amount of space in the angle and the ultrasound component may also have an effect in increasing outflow. Interestingly, some patients also have an increase in IOP after surgery and some patients have no change in IOP after surgery.

The iStent is a FDA and HSA approved micro-bypass stent device that bypasses the trabecular meshwork (filtration membrane of the aqueous fluid exit pathway) and reroutes aqueous from the anterior chamber directly into canal of Schlemm and out of the eye. It lowers the IOP by increasing the outflow of fluid from the eye from the micro-bypass. In angle closure, the lens has to be removed to create enough space for the iStent to be inserted.

We therefore plan to compare the effects of phacoemulsification alone, to phacoemulsification with iStent implantation in patients with angle closure and angle closure glaucoma.

If the IOP can be better controlled with the phaco + iStent, then it can reduce the need for IOP lowering medications, and reduce the need for further invasive glaucoma surgery such as trabeculectomy, that have higher risks of adverse events.

We will perform a randomised controlled study, blinded to the patient and the IOP checking staff. Our hypothesis is that the phaco-iStent combined group will have a lower mean IOP at 1 year compared to the phacoemulsification alone group and that more patients will have an IOP of <21mmHg at 1 year in the combined phaco-iStent group, and the phaco-iStent group will require less medications at 1 year.

### a. Rationale for the Study Purpose

Phacoemulsification alone reduces the IOP in the first year, but tends to return to baseline after 1-2 years. A meta-analysis comparing phacoemulsification with phacoemulsification with iStent found it to be in favour to the phacoemulsification with iStent group (SMD=-0.46). There have been 4 randomised controlled trials comparing phacoemulsification with phacoemulsification + iStent in primary open angle glaucoma and 6 studies evaluating phacoemulsification + iStent again in open angle glaucoma. The four randomised controlled trials showed the phaco+iStent group to have a greater IOP reduction. (17% vs 9%, 27% vs 16%, 10% vs 8%, 8% vs 5%)
There have been no studies evaluating phacoemulsification + iStent in primary angle closure

or primary angle closure glaucoma.

This study will be the first randomised controlled trial in primary angle closure or primary angle closure glaucoma. This will also be the first iStent trial in Singapore on Singaporeans.

This is important because primary angle closure is much more common in the Singaporean Chinese population and the most common cause of irreversible bilateral blindness in the Asia. Phacoemulsification has become a more common procedure to help manage this condition although trabeculectomy or combined phacotrabeculectomy is still the gold standard surgery. Phacoemulsification with iStent may be a suitable operation for this condition that can avoid the higher risks of the trabeculectomy and yet have a better IOP control than phacoemulsification alone.

### b. Rationale for Doses Selected

Phacoemulsification with 1 iStent will be used because in the open angle studies, it had a improved IOP control compared to phacoemulsification alone. 2 iStents or 3 iStents can be inserted and have been reported to have good response, but with very limited data to show any added benefit given the additional cost.

### c. Rationale for Study Population

The patients will be selected from the clinic patient population. Primary angle closure and primary angle closure glaucoma have been chosen because the disease is more relevant and common in the Singaporean context compared to the western countries. Also this disease has not been studied using the iStent.

### d. Rationale for Study Design

Randomised controlled trial with blinding to the patient and the IOP measurer and reader with adequate sample size to compare both groups is the best way to answer our research question.

## 2. HYPOTHESIS AND OBJECTIVES

### 2.1. Hypothesis

Phacoemulsification with micro-bypass stent has a better IOP lowering effect compared to phacoemulsification alone in primary angle closure and primary angle closure glaucoma at 1 year after surgery.

### 2.2. Primary Objectives

To assess the efficacy of the iStent trabecular micro-bypass stent (Glaukos Corporation, Laguna Hills, CA) in combination with cataract surgery in subjects with primary angle closure and mild to moderate primary angle closure glaucoma

## 2.3. Potential Risks and benefits:

### a. End Points – Efficacy

The primary outcome is: unmedicated IOP</=21mmHg at 1 year and mean IOP at 1 year.
A secondary outcome measure is medication reduction at 1 year post operation

### b. End Points - Safety

Safety measures include best corrected visual acuity, slit lamp observations, complications and adverse events

## 3. STUDY POPULATION

### 3.1. List the number of subjects to be enrolled.

All patients will be recruited from the ophthalmology and visual science department of Khoo Teck Puat Hospital. There will be no restriction on race. Children will be excluded from this study as the surgeons have limited experience operating on children.

The project aims to recruit 32 patients, 16 in each arm of the randomisation, of phacoemulsification alone and phacoemulsification and iStent Implant.

### 3.2. Criteria for Recruitment

The subjects will be assessed in the clinic to confirm whether they meet the eligibility criteria and may be enrolled.
Subjects will be invited to participate in the study if they are to be listed for phacoemulsification with lens implantation and meet the inclusion criteria. If the subject expresses interest, then the informed consent form will be given to the subject to read.

### 3.3. Inclusion Criteria

Provide informed consent
Previous diagnosis of PAC or PACG
IOP above 21mmHg at 3 separate visits
On 1 or more hypotensive medications
Pre-operative VA of no better than 6/12

### 3.4. Exclusion Criteria

Other glaucoma diagnosis: POAG, secondary glaucoma
PAS in the nasal and inferior quadrant
Cloudy cornea
Previous glaucoma surgery
History of trauma

Ocular surface disease
Pre-proliferative or proliferative diabetic retinopathy
Age related macular degeneration with macular scar or macular atrophy

### 3.5. Withdrawal Criteria

Complication during phacoemulsification including posterior capsular tear or vitreous loss.
Surgeon is unable to insert the iStent during surgery
Patient request to be withdrawn

### 3.6. Subject Replacement

There will be no replacement.

## 4. TRIAL SCHEDULE

**Part of research Schedule:**

Patients who meet the inclusion criteria will be invited to participate in this study.Patient will be randomly assigned to either phacoemulsification alone, or phacoemulsification with iStent by random envelope shuffle technique.

After operation the patient will be followed up at day 1, week 1, week 2, months 1, 3, 6 and 12.

At each visit the patient will have the following tests: Tonometry (IOP check) - Not to be taken by the operating surgeon, to be taken by 2 people, one IOP checker and one reader.

**Part of Standard of Care:**
At each visit:
Visual Acuity, Slit lamp examination and Fundoscopy.
At 6 monthly intervals:
Visual field examination

## 5. STUDY DESIGN

Single centre, randomised prospective trial, the patient and the IOP checking staff will be blinded. Ranomised by random envelope shuffle technique.
1:1 ratio allocation

2 arms: phacoemulsification alone and phacoemulsification and iStent.
16 patients in each arm, 32 patients in total.

The post-operative management is the same for both arms
After operation the patient will be followed up at day 1, week 1, week 2, months 1, 3, 6 and 12.

At each visit the patient will have the following tests: Tonometry (IOP check) - Not to be taken by the operating surgeon, to be taken by 2 people, one IOP checker and one reader.

The target IOP is 18mmHg for patients with PAC or mild PACG. If the IOP rises above 18mmHg in 2 consecutive visits then the original glaucoma medication(s) will be reinstated or as per the clinicians discretion.

IOP at 12 months will be the primary outcome measure. The target pressure will be based on the Asia Pacific Glaucoma Guidelines. For PAC with high IOP and PAS and early PACG, the target will be >/=20% from base line or 18mmHg whichever is lower. b. The Asia Pacific Glaucoma Guidelines classifies "PAC with High IOP and PAS" to be "glaucoma with moderate 5-year risk for visual loss" and to treat the IOP with a target of >/=20% or 18mmHg whichever is lower.

The target IOP is 18mmHg for patients with PAC or mild PACG. If the IOP rises above 18mmHg in 2 consecutive visits then the original glaucoma medication(s) will be reinstated or as per the clinicians discretion.

The patient will be masked to the treatment arm given, but the investigators will not be masked.

The procedure will be performed by 2 surgeons: Dr Sangtam Tiakumzuk and Dr Jason Cheng, the follow up visits and monitoring of pressure will be done by the investigation team.

### 5.1. Summary of Study Design

Briefly describe the study design and indicate, in general terms, how the design will fulfil the intent of the study.

Single centre, randomised prospective trial, the patient and the IOP checking staff will be blinded. Randomised by random envelope shuffle technique.
2 arms: phacoemulsification alone and phacoemulsification and iStent.
16 patients in each arm, 32 patients in total.

The equal allocation 1:1 ratio will help determine which arm is more efficacious. The regular follow up will determine the safety of the iStent device. The randomisation will avoid surgical bias. The blinding of the patient and IOP measuring staff will avoid observational bias.

## 6. METHODS AND ASSESSMENTS

2 arms: phacoemulsification alone and phacoemulsification and iStent to compare the results of both arms in terms of IOP at one year.

No film or video taping will be used for this study.

### 6.1. Randomisation and Blinding

This section should describe randomisation and blinding procedures (if applicable to the

study design). Include a description or a table that describes how study subjects will be assigned to the study groups. The timing and procedures for planned and unplanned breaking of randomization codes should be included. Include statement when unmasking may occur and who may unmask.

Randomised controlled study. 1:1 ratio allocation32 patients16 phacoemulsification alone16 phacoemulsification with iStent Randomisation by shuffled envelope system.
Follow up will be at 1 day, 1 week, 1 month, 3 months, 6 months, 1 year after surgery.
Patient will be blinded to the procedure.
The IOP measure and reader will be blinded to the procedure.

There will be no planned breaking of randomisation.
Unplanned breaking will happen if any envelopes are damaged or lost.

Unmasking will take place after 1 year post operation by the study team to inform the patient of the procedure.

## 6.2. Contraception and Pregnancy Testing

For females of childbearing age will be asked if they are pregnant.

## 6.3. Study Visits and Procedures

Provide a brief outline of the all the study visits, procedures to be done during the study, follow up after the study and discontinuation visit.

*a. Screening Visits and Procedures*

No formal screening visit.
The patient will be identified in clinic and be invited to participate in the trial.
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*b. Study Visits and Procedures*

Patients who meet the inclusion criteria will be invited to participate in this study. Patient will be randomly assigned to either phacoemulsification alone or phacoemulsification with iStent by random envelope shuffle technique.

After operation the patient will be followed up at day 1, week 1, week 2, month 1, months 3, 6 and 12.

At each visit the patient will have the following tests:Tonometry (IOP check) - Not to be taken by the operating surgeon, to be taken by 2 people, one IOP checker and one reader.

*c. Final Study Visit:*

Final visit will be at 1 year after surgery.
Patient will be informed of the procedure performed.
They will resume normal follow up in the clinic for their glaucoma.

*d. Post Study Follow up and Procedures*

At each visit the patient will have the following tests: Tonometry (IOP check) - Not to be taken by the operating surgeon, to be taken by 2 people, one IOP checker and one reader.

As part of their routine assessment they will be examined for evidence of complications related to the operation.

*e. Discontinuation Visit and Procedures*

Subjects may withdraw voluntarily from participation in the study at any time.
They will be unmasked regarding the procedure performed. They will need to continue to have the same follow up schedule because it is the same standard of care, except that at each visit they will have tonometry taken by the same doctor (instead of a two person technique) in the clinic who will not be blinded to their operation status.

Subjects may also withdraw voluntarily from receiving the study intervention for any reason. If the patient does not have the operation, then they will receive the standard management for their condition which is usually 6 monthly follow up if their condition is stable.

## 7. TRIAL MATERIALS

iStent is a micro-bypass stent made of titanium that is FDA and HSA approved. It is inserted into the Schlemm's canal to by pass the trabecular meshwork to improve outflow of aqueous eye fluid and lower IOP.
The control arm is phacoemulsification, which is an operation that removes the lens of the eye and replaces it with a intra ocular lens. It is the standard of care for cataracts but not standard of care for primary angle closure and primary angle closure glaucoma. However, phacoemulsification has been shown to have a beneficial effect on the drainage angle and IOP in primary angle closure and primary angle closure glaucoma.

### 7.1. Trial Product (s)

The iStent is a micro-bypass stent made of titanium and is inert inside the eye. The istent is designed to stay in the eye and does not need to be removed.

Here are the reported complications related to iStent insertion:

- Stent occlusion
- Hyphaema
- IOP elevation more than 10mmHg
- Stent malposition
- Subconjunctival haemorrhage
- iritis

### 7.2. Storage and Drug Accountability

iStent needs to be stored in room temperature.

## 8. TREATMENT

### 8.1. Rationale for Selection of Dose

NA

### 8.2. Study Drug Formulations

NA

### 8.3. Study Drug Administration

NA

### 8.4. Specific Restrictions / Requirements

NA

### 8.5. Blinding

Patient will be blinded to the procedure.
The IOP measure and reader will be blinded to the procedure.

### 8.6. Concomitant therapy

NA

## 9. SAFETY MEASUREMENTS

### 9.1. Definitions

Reporting procedures for:

- Deaths and life threatening events
- other SAEs: Hospitalisation events.
- Other adverse events

**Standard procedures for reporting adverse events**
Information regarding adverse events (including incidence, duration, seriousness, severity, relationship to treatment and action taken) will be recorded throughout the one year of the study. If adverse events occur, the first concern will be the safety of the study participants.

### 9.2. Collecting, Recording and Reporting of "Unanticipated Problems Involving Risk to Subjects or Others" – UPIRTSO events to the NHG Domain Specific Review Boards (DSRB)

An adverse event is defined as any untoward medical occurrence in a patient administered a therapeutic treatment and that does not necessarily have a causal relationship with this

treatment. An adverse event (AE) can therefore also be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a therapeutic treatment, whether or not related to the therapeutic treatment.

Any adverse event is to be recorded on the appropriate case report form. These will be graded by an Investigator at each site for severity and relationship to study treatment. The severity should be completed using the following definitions as guidelines:

Mild: Awareness of sign or symptom, but easily tolerated.
Moderate: Discomfort enough to cause interference with usual activity.
Severe: Incapacitating with inability to work or do usual activity.
Not applicable: In some cases, an adverse event may be an 'all or nothing' finding which cannot be graded.

To determine the relationship (if any) between an adverse event and the study drug a causal relationship is deemed present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug.

All adverse events that are therapy related and unexpected should also be reported to the Institutional Review Board.

Procedure for reporting Serious Adverse Events
A Serious Adverse Event is defined as any adverse event occurring that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. All serious adverse events should be reported to the Institutional Review Board.

## 9.3. Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to the Health Science Authority (HSA)

Reporting of adverse events involves the Principal Investigator submitting to the approving CIRB the completed SAE Reporting Form within the stipulated timeframe. The Principal Investigator is responsible for informing the institution representatives or regulatory bodies as required and appropriate.

"A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- Results in death.
- Is life-threatening (immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.

- Results in persistent or significant disability/incapacity.
- Results in congenital anomaly/birth defect.
- Is a Medically important event.

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and/or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious."

All SAEs that are unexpected and related to the study device will be reported. The investigator is responsible for informing HSA no later than 15 calendar days after first knowledge that the case qualifies for expedited reporting. Follow-information will be actively sought and submitted as it becomes available. For fatal or life-threatening cases, HSA will be notified as soon as possible but no later than 7 calendar days after first knowledge that a case qualifies, followed by a complete report within 8 additional calendar days.

### 9.4. Safety Monitoring Plan

Safety monitor is Dr Ben Chang – Senior Consultant in Ophthalmology, Khoo Teck Puat Hospital

### 9.5. Complaint Handling –

Complaints will be handled by the principal investigator

### 9.6. Potential Risks

The potential risks to the patient specific to the iStent are:
The iStent has risks of IOP spikes, infection, bleeding in the anterior chamber and iStent dislocation.
The potential risks to the patient specific to the phacoemulsification are:
Infection, bleeding, reduced vision, inflammation, posterior capsular rupture, vitreous loss, retinal detachment, endophthalmitis, suprachoroidal haemorrhage and IOL dislocation.

## 10. DATA ANALYSIS

### 10.1. Data Quality Assurance

Data management will be handled by the principal investigator and co-investigators. Patient data obtained for this study will be entered in electronic format. Accuracy checked will be performed by the investigators who will be cleaning the data entered from time to time.

### 10.2. Data Entry and Storage

Research data will be stored on a laptop that is password encrypted and locked to a desk in a

secure office in Khoo Teck Puat Hospital.

## 11. SAMPLE SIZE AND STATISTICAL METHODS

### 11.1. Determination of Sample Size

Details on sample size calculation and the means by which data will be analysed and interpreted.
In particular, specify all of the following:

- Null Hypothesis
  Phacoemulsification with micro-bypass stent has no difference in effect on IOP compared to phacoemulsification alone in primary angle closure and primary angle closure glaucoma at 1 year after surgery.
- Alternate hypothesis
  Phacoemulsification with micro-bypass stent has a better IOP lowering effect compared to phacoemulsification alone in primary angle closure and primary angle closure glaucoma at 1 year after surgery.
- Type I error rate = 0.05
- Type II error rate = 0.2

**Sample Size Calculation:**
**Based on published data of phaco and phaco iStent RCT in open angle glaucoma:**
Mean IOP for control at 1 year (phaco only group) – 19.2mmHg+/- 3.1
Mean IOP for combined group at 1 year (phaco+istent group) – 16.6mmHg +/-3.5
Alpha = 0.05
Power = 0.80
SD: 2.4
Difference: 2.6
**Sample size = 14 in each arm**

### 11.2. Statistical and Analytical Plans

*a. General Considerations*
Independent t- tests will be used to compare both groups at 12 months post operation

"Success" will be defined as IOP unmedicated IOP</=21mmHg at 1 year and unmedicated IOP reduction of >/=20% at 1 year, with no additional anti-glaucomatous medications at 1 year. The rational for 20% reduction is based on published RCT trials that use 20% as a standard reduction expected from this device. The same reduction percentage is used for comparison to other published data.

Chi-square test will be used to compare success versus failure in both groups.

## 12. ETHICAL CONSIDERATIONS

### 12.1. Informed Consent

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Singapore Good Clinical Practice and the applicable regulatory requirements.

This study protocol, including the Patient Information and Informed Consent Form, will be approved in writing by the Centralised Institutional Review Board (CIRB) prior to enrolment of any patient into the study.

The principle investigator will inform the CIRB of any amendments to the protocol or other study-related documents, as per local requirement.

Informed Consent
The nature, purpose and risk of the study will be explained to the patients by Investigators. Patients will be given opportunities to ask questions and all queries will be answered prior to written consent is taken. During the informed consent process, the study team will comply with the SGGCP guidelines and to the ethical principles that have their origin in the Declaration of Helsinki.

### 12.2. IRB review

This study protocol, including the Patient Information and Informed Consent Form, will be approved in writing by the Centralised Institutional Review Board (CIRB) prior to enrolment of any patient into the study.

### 12.3. Confidentiality of Data and Patient Records

Following will be done to ensure confidentiality of Data and Patient Records,

- Login credentials (user-IDs and passwords) are required when logging into Alexandra Health networks and shared information systems.
- Research data on laptops are password protected and locked to a desk in a secure office in the hospital.
- Computers, laptops, and all files and documents containing patient data will be secured in secure office.
- Only delegated members from the study team will be allowed to access to patient data related to this study.

## 13. PUBLICATIONS

This study will adhere to NMRC's policy on Publications of Results and Findings.

## 14. RETENTION OF TRIAL DOCUMENTS

Records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, results of consultations, etc.) as well as IRB records and other regulatory documentation will be kept in a secure storage facility at each study site. Only delegated personnel in the study team will be given access to these data. Data collected from will be anonymized before entered electronically. All records will be accessible for inspection and copying by authorized authorities.

In accordance to SG-GCP, the essential documents will be retained until

- at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications; or
- at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product; or
- 6 years after the completion of the clinical trial